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Somite and Brain Nociceptive Coupling in Evolution of Nociceptive-Sympathetic Coupling for Pain Sensations by NBA

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Abstract

In May 2016, it was proposed by the US athletes of the National Basketball Association (NBA) on television that the nociceptive-sympathetic coupling be required for pain sensations. Later, it was demonstrated that, via the activation of sympathetic outputs directly by the nociceptive neurons in laminae I and V of the dorsal spinal horn as well as those in periaqueductal grey (PAG) of brain, it was completed the nociceptive-sympathetic coupling in vertebrates. In this article, for the evolutionary variations in both brain complexity and autonomic regulation in various animals, it is transformed this nociceptive-sympathetic coupling into more general forms for the evolutionary perspectives. Herein, it is classified the nociceptive-sympathetic coupling for pain sensations from the spinal cord as the somite nociceptive coupling, and the nociceptive-sympathetic coupling from PAG as the brain nociceptive coupling. Because of the wide presence of nociception in almost all vertebrates and invertebrates, such division of somite and brain nociceptive coupling makes it possible to demonstrate the presence of individual couplings in various animals including the primitive amphioxus, Drosophila and so on. In reverse, via evolution, the well-evidenced presence of somite nociceptive coupling in Drosophila supports the widely neglected nociceptive-sympathetic coupling for pain sensations at the spinal cord in vertebrates.

Subject Areas

Neuroscience, Anaesthesiology & Pain Management, Anatomy & Physiology, Evolutionary Studies

Keywords

Pain, Autonomic Regulation, Somite Nociceptive Coupling, Brain Nociceptive Coupling, Drosophila, Evolution

1. Introduction

On May 6, 2016, the US athletes in the games of the National Basketball Association (NBA) on television proposed that the nociceptive sensations could be relayed from the nociceptive-sympathetic coupling [1] [2]. Later, it was demonstrated that the nociceptive neurons in laminae I and V of the dorsal spinal horn as well as the nociceptive neurons in periaqueductal grey (PAG) of brain might directly activate the sympathetic outputs in vertebrates [2], thus completing the neural circuits responsible for the nociceptive-sympathetic coupling. However, it is present the evolutionary variations in both brain complexity and autonomic regulation in various animals. In this article, it is attempted to transform this nociceptive-sympathetic coupling mechanism in vertebrates into more general forms to fit more animal species beyond vertebrates, so as to reveal the evolutionary perspectives for the nociceptive-sympathetic coupling hypothesis of pain sensations.

2. Method

In this article, it is adopted the method of reviewing relevant fields of studies for demonstration and integration. It is cited the updated relevant reviews or, if not available, salient and repeated experimental results in subfields, and then integrated to review and demonstrate. It is necessary to clarify that the presently widely utilized meta-analysis fits investigation of a specific topic in a well-studied subfield, but not for integration or summarization from several fields like this paper.

Papers were searched out from Pubmed and Baidu Xueshu. The updated relevant reviews in subfields were given priority to cite. If not available, relevant reviews were cited. If still unavailable, the salient and repeated experimental results of original articles in subfields were cited. The papers written by the author were cited with priority above all of these so as to demonstrate the expertise of the author to write this article.

3. The Neural Pathways for the Hypothetic Nociceptive-Sympathetic Coupling

3.1. The Present Feedback Circuits for Pain Transmission in Spinal Cord

In mammals, the primary afferent neurons located in dorsal root ganglion (DRG) deliver the peripheral sensory information via the dorsal root (or posterior root) to the spinal cord with three types of afferent fibers, the Aß-fibers, Aδ-fibers, and C-fibers [3] [4] [5].

Aß-fibers relay the tactile information, large in diameter and low in activation thresholds [3] [4] [5]. Both Aδ- and C-fibers possess nociceptors [4] [5], while relay the mechanical, thermal, nociceptive and chemical stimuli, small in diameter and high in activation thresholds [3] [4] [5]. The Aδ-fibers form synapses onto the laminae I, II and V of spinal dorsal horn [5] [6], while the C-fibers onto

the laminae I and II [5] [6]. The laminae I, II and V in spinal dorsal horn are responsible for relaying the nociceptive inputs.

Many nociceptive neurons in lamina I of spinal dorsal horn fruther project to several brain regions, such as the caudal ventrolateral medulla (CVLM), periaqueductal grey (PAG), parabrachial area (PB) and so on [5] [6]. The PAG neurons can activate the neurons of rostral medullary raphe nuclei [7] [8], while the raphe serotonergic (5-HT) neurons in turn project to the spinal nociceptive neurons and inhibit their activities, suppressing onto the spinal pain transmission and completing the feedback circuits for pain transmission in spinal cord [5] [7] [8].

3.2. The Neural Pathways of the Nociceptive-Sympathetic Coupling

On May 6, 2016, the US athletes of NBA in television proposed the nociceptive-sympathetic coupling hypothesis for pain sensations [1] [2]. The sympathetically maintained pain such as causalgia and reflex sympathetic dystrophy can support the nociceptive-sympathetic coupling [9] [10].

Recently, Cai wrote an article depicting the neural pathways for the nociceptive-sympathetic coupling [2]. One the one hand, it was shown that the muscular sympathetic nerve was coupled in activity to PAG notably and a few others in brain for sustained muscle pain [11], the tonic glutamatergic inputs from PAG to rostral ventrolateral medulla (RVLM) were increased for the high blood pressure of neuropathic pain [12], and the cardiac sympathetic activation eliciting pain activated the PAG, PB, dorsal raphe, and locus coeruleus (LC) in brain [13], all demonstrating the links of brain PAG to the sympathetic effects of pain [2]. On the other hand, more importantly but neglected widely by most pain researchers nowadays, it was demonstrated that not only the sympathetic preganglionic neurons received afferents directly from the nociceptive lamina I [14] and V [15] in spinal dorsal horn, but also could be activated by these spinal nociceptive neurons [16] [17], direct completing the nociceptive-sympathetic coupling at the spinal cord [2].

In addition to the nociceptive-sympathetic coupling, it was also depicted the nociceptive-respiratory coupling [2] [18], which was mediated via PB in brain rather than the spinal cord or brain PAG.

In brief, the direct sympathetic links from the nociceptive neurons in laminae I and V of dorsal spinal horn as well as the nociceptive neurons in periaqueductal grey (PAG) of brain complete the neural pathways for nociceptive-sympathetic coupling in vertebrates.

4. The Somite and Brain Nociceptive Coupling in Evolution

4.1. The Wide Presence of Nociceptive Sensations in Animals

The neural pathways for nociceptive-sympathetic coupling were revealed in mammals [2] including humans. To consider the evolutionary perspectives of

nociceptive-sympathetic coupling, it is certainly necessary to first consider the presence of pain sensations in other animals than mammals.

The spinal cord, PAG and PB for nociceptive-sympathetic coupling and nociceptive-respiratory coupling are all located in the central nervous system below thalamus, and are ancient and primitive in vertebrates during evolution [2]. Indeed, pain sensations exist in various vertebrates, including the early fishes [2] [19] [20] [21]. Neuronal responses have been shown in spinal cord, cerebellum, tectum, and telencephalon in both goldfish and trout for mechanoceptive brush and nociceptive pin-prod [21], indicating both spinal cord and brain responsible for pain sensations. Whereas, because the lung has emerged after amphibians while fishes adopt the gill to breathe, the nociceptive-respiratory coupling via PB neurons may be different in fishes [2].

In the step further, it is certainly necessary to consider the presence of pain sensations in animals more ancient and primitive than vertebrates. Because of the variations of central neural structures in invertebrates and primitive vertebrates, the biochemical perception and neural transmission of nociception become the key marks for assaying the pain sensations in these ancient and primitive animals.

Nociceptors or nociceptive neural transmission has been discovered throughout the Animalia kingdom, such as Annelida [22] [23], Mollusca including Aplysia [22] [23], Nematoda including C elegans [23] [24], Arthropoda including Drosophila [22] [23], Cephalochordata including amphioxus [25], Agnatha including lamprey [26], Vertebrata including fishes [2] [19] [20] [21] and mammals [5] [7] [8], and so on. Therefore, pain sensations are widely present in almost all animals, even including those emerging early in evolution at least as ancient and primitive as Annelida.

4.2. The Classification of Somite and Brain Nociceptive Coupling

In invertebrates and primitive vertebrates, the evolutionary variations in both brain complexity and autonomic regulation occur in various primitive animals, making them dramatically different from those in higher vertebrates. In this regard, the neural structures employed in nociceptive-sympathetic coupling may not be found in these primitive animals, just as the nociceptive-respiratory coupling via PB neurons may be different in fishes lack of lung [2]. Because of such discrepancies, to reveal the pain mechanisms in invertebrates and primitive vertebrates, it is necessary to transform the nociceptive-sympathetic coupling mechanism into more general forms.

The nociceptive-sympathetic coupling in vertebrates comprises the direct coupling of the nociceptive neurons in laminae I and V of dorsal spinal horn to the sympathetic output [2], and the coupling of nociceptive neurons in periaqueductal grey (PAG) of brain to the sympathetic effects [2]. The spinal cord and PAG are specific neural structures in vertebrates, belonging to the peripheral somite and anterior brain respectively. On the other hand, the peripheral somite and anterior brain are general structures present in all vertebrates and most

invertebrates more advanced than those in Annelida. In this regard, to correspond and compare the nociceptive-sympathetic coupling in vertebrates to the pain mechanism in invertebrates, it is neccesary to make use of the more general structures as peripheral somite and anterior brain rather than spinal cord and PAG respectively. Accordingly, it is herein classified the nociceptive-sympathetic coupling for pain sensations from spinal cord as the somite nociceptive coupling, and the nociceptive-sympathetic coupling from PAG of brain as the brain nociceptive coupling, respectively (Table 1). With the peripheral somite and anterior brain as general structures present in all vertebrates and most invertebrates more advanced than those in Annelida, it is possible to consider the suitability for the somite and brain nociceptive coupling in primitive vertebrates and invertebrates.

4.3. The Nociceptive Coupling in Amphioxus, Drosophila and C Elegans

Updated progressions from abundant investigations of noxious perceptions on several model animals would help determine the suitability for the somite and brain nociceptive coupling in primitive animals, notably in amphioxus, Drosophila and C elegans.

1) Amphioxus: Amphioxus is important in that it is the key animal evolving from invertebrates to vertebrates. Unfortunately, the nociceptive research in amphioxus is very few. Up to now, only gene analysis of Rfamide neuropeptide suggested its plausible nociceptive function [25]. Whereas, because nociceptions have been identified in such invertebrates as Drosophila [22] [23] and C elegans [23] [24] as in vertebrates, it is certain that the nociception must also exist in amphioxus between the invertebrates and vertebrates.

2) Drosophila: Extensive investigations have been performed in Drosophila for revealing the neural mechanism of nociceptive reactions in this animal species [22] [23]. Notably, it was reported that the class IV dendrite arborization (C4 da) sensory neurons in the peripheral nervous system were responsible for perception of multiple nociceptive modalities, and then activated the segmentally arrayed local interneurons (medial clusters of C4 da second-order interneurons [mCSIs]) in the ventral nerve cord that were necessary and sufficient to trigger rolling behavior [27]. Likewise, it was also shown that a population of interneurons in the nerve cord of Drosophila, termed Down-and-Back (DnB)

Table 1. The somite and brain nociceptive coupling.

Type	Vertebrate nociceptive-sympathetic coupling	Spatial segment of nociceptive coupling	Division of nociceptive coupling
Somite	Coupling at spinal cord	Peripheral somite	Somite nociceptive coupling
Brain	Coupling at PAG of brain	Anterior brain	Brain nociceptive coupling

neurons, were activated by noxious heat, promoted nociceptive behavior, and were required for robust escape responses to noxious stimuli [28]. Obviously, the interneurons in the nerve cord of Drosophila in both of the two reports corresponded to the somite nociceptive coupling. In a more recent report, complex reactions to graded encodings of noxious stimuli relied on the neural circuits across segments [29]. More investigations are required to demonstrate the inter-segmental brain nociceptive coupling in Drosophila.

3) C elegans: There have also been many investigations in C elegans for nociceptive reactions in this simple primitive animal species [23] [24]. Especially, the noxious sensory neuron PVD and interneuron ALA are both long, covering the majority of body length of the small C elegans, with the interactions between PVD and ALA across several segments [30]. Obviously, the somite nociceptive coupling exists in the PVD and ALA coupling, while whether the anterior portion of ALA lack of PVD inputs can transfer noxious stimuli as brain nociceptive coupling to coordinate behavioral responses deserves more investigations.

In all, delicate researches on the neural circuits for responses to noxious stimuli in both Drosophila and C elegans have confirmed the widespread occurrence of somite nociceptive coupling in invertebrates, while the brain nociceptive coupling in invertebrates requires more investigations.

5. Discussions

In this article, it is first reviewed the recently depicted neural pathways underlying the nociceptive-sympathetic coupling hypothesis proposed by the US athletes of National Basketball Association (NBA) in television [2]. The nociceptive neurons in laminae I and V of dorsal spinal horn as well as those in periaqueductal grey (PAG) of brain activate the sympathetic outputs to complete the nociceptive-sympathetic coupling in vertebrates [2].

Because of the evolutionary variations in both brain complexity and autonomic regulation in various animals, the neural structures involved in the neural pathways for nociceptive-sympathetic coupling in vertebrates may not be present in invertebrates. Due to the universal presence of nociceptive sensations in almost all vertebrates and invertebrates, to correspond and compare the pain mechanisms in the simpler primitive animals, in this article it is adopted the peripheral somite, the bodily segment widely present in vertebrates and invertebrates, to term the nociceptive-sympathetic coupling from spinal cord as somite nociceptive coupling, while it is adopted the anterior brain widely present in vertebrates and invertebrates to term the nociceptive-sympathetic coupling from brain PAG as brain nociceptive coupling (**Table 1**).

Thereafter, in this article it is considered the evolutionary perspectives for the division of somite and brain nociceptive coupling in primitive vertebrates and invertebrates, especially in several model animals notably as amphioxus, Drosophila and C elegans.

In amphioxus, nociceptive research is few, only with gene analysis of Rfamide neuropeptide to suggest its plausible nociceptive function [25]. As this animal is

the key evolving to vertebrates from invertebrates, the nociceptive function of amphioxus is inferred from the confirmed nociceptions in invertebrates such as Drosophila [22] [23] and C elegans [23] [24], and in vertebrates including the fishes [2] [19] [20] [21].

In Drosophila, the nociceptive interneurons notably as mCSIs [27] and DnB [28] in the nerve cord of Drosophila fit well with the somite nociceptive coupling mechanism, while the brain nociceptive coupling in Drosophila requires further investigation. Of special importance is that, from evolutionary perspectives, the somite nociceptive coupling in Drosophila strongly supports the nociceptive-sympathetic coupling from spinal cord in vertebrates for pain sensations, which has been neglected up to now until Cai recently delineated this nociceptive-sympathetic pathway in support to the nociceptive-sympathetic coupling hypothesis of pain sensations from NBA [2].

In C elegans, the noxious sensory neuron PVD and interneuron ALA, with their interactions across several segments [30], manifest the somite nociceptive coupling, with the brain nociceptive coupling requiring more investigations.

Obviously, further dividing the nociceptive-sympathetic coupling into the somite and brain nociceptive coupling helps extend the evolutionary perspectives for pain mechanisms across various animals, from vertebrates to invertebrates. Meanwhile, the well evidenced presence of somite nociceptive coupling in Drosophila in turn helps support the nociceptive-sympathetic coupling from spinal cord for pain sensations in vertebrates [2].

6. Limitations

The division of somite and brain nociceptive coupling is only applicable to animals with the division of anterior brain and nerve cord, but not the more primitive animals without a brain at all. Besides, the presence of brain nociceptive coupling in invertebrates requires further investigation. Finally, the various animal species selected for nociceptive research need to increase, as exemplified by the lack of sufficient data for amphioxus in this article.

7. Conclusion

In this article, based on the recently delineated neural pathways in support of the hypothetic nociceptive-sympathetic coupling of pain sensations from NBA, it is classified the nociceptive-sympathetic coupling from the spinal cord as the somite nociceptive coupling, while the nociceptive-sympathetic coupling from brain PAG as the brain nociceptive coupling. From evolutionary perspectives, division of somite and brain nociceptive coupling fits the common structures widely present in both vertebrates and most invertebrates more advanced than those in Annelida. It is attempted to correspond the progressions in research of nociception in amphioxus, Drosophila, and C elegans to the somite and brain nociceptive coupling, and concluded that the somite nociceptive coupling is evidently present in Drosophila. In reverse, the presence of somite nociceptive

coupling in Drosophila supports the widely neglected nociceptive-sympathetic coupling from the spinal cord for pain sensations in vertebrates.

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Conflicts of Interest

The author declares no conflict of interest for this work.

References

[1] Cai, Z.-J. (2016) The Hypothetic Post-Sensory Nociceptive-Sympathetic Coupling Necessary for Pain Sensation from NBA. *Journal of Neurology and Neuroscience*, **7**, 141. https://doi.org/10.21767/2171-6625.1000141

[2] Cai, Z.-J. (2019) The Neural Pathways for the Hypothetic Nociceptive-Sympathetic Coupling of NBA for Pain Sensation. *Open Access Library Journal*, **6**, e5780. https://doi.org/10.4236/oalib.1105780

[3] Lawson, S.N. (2002) Phenotype and Function of Somatic Primary Afferent Nociceptive Neurones with C-, Adelta- or Aalpha/beta-Fibres. *Experimental Physiology*, **87**, 239-244. https://doi.org/10.1113/eph8702350

[4] Haggard, P., Iannetti, G.D. and Longo, M.R. (2013) Spatial Sensory Organization and Body Representation in Pain Perception. *Current Biology*, **23**, R164-R176. https://doi.org/10.1016/j.cub.2013.01.047

[5] D'Mello, R. and Dickenson, A.H. (2008) Spinal Cord Mechanisms of Pain. *British Journal of Anaesthesia*, **101**, 8-16. https://doi.org/10.1093/bja/aen088

[6] Todd, A.J. (2002) Anatomy of Primary Afferents and Projection Neurones in the Rat Spinal Dorsal Horn with Particular Emphasis on Substance P and the Neurokinin 1 Receptor. *Experimental Physiology*, **87**, 245-249. https://doi.org/10.1113/eph8702351

[7] Basbaum, A.I. and Fields, H.L. (1978) Endogenous Pain Control Mechanisms: Review and Hypothesis. *Annals of Neurology*, **4**, 451-462. https://doi.org/10.1002/ana.410040511

[8] Mayer, D.J. (1984) Analgesia Produced by Electrical Stimulation of the Brain. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **8**, 557-564. https://doi.org/10.1016/0278-5846(84)90015-0

[9] Roberts, W.J. (1986) A Hypothesis on the Physiological Basis for Causalgia and Related Pains. *Pain*, **24**, 297-311. https://doi.org/10.1016/0304-3959(86)90116-8

[10] Gibbs, G.F., Drummond, P.D., Finch, P.M. and Phillips, J.K. (2008) Unravelling the Pathophysiology of Complex Regional Pain Syndrome: Focus on Sympathetically Maintained Pain. *Clinical and Experimental Pharmacology and Physiology*, **35**, 717-724. https://doi.org/10.1111/j.1440-1681.2007.04862.x

[11] Kobuch, S., Fazalbhoy, A., Brown, R., Macefield, V.G. and Henderson, L.A. (2018) Muscle Sympathetic Nerve Activity-Coupled Changes in Brain Activity during Sustained Muscle Pain. *Brain and Behavior*, **8**, e00888. https://doi.org/10.1002/brb3.888

[12] Wang, W., Zou, Z., Tan, X., Zhang, R.W., Ren, C.Z., Yao, X.Y., Li, C.B., Wang, W.Z. and Shi, X.Y. (2017) Enhancement in Tonically Active Glutamatergic Inputs to the Rostral Ventrolateral Medulla Contributes to Neuropathic Pain-Induced

High Blood Pressure. *Neural Plasticity*, **2017**, Article ID: 4174010. https://doi.org/10.1155/2017/4174010

[13] Guo, Z., Li, P. and Longhurst, J.C. (2002) Central Pathways in the Pons and Midbrain Involved in Cardiac Sympathoexcitatory Reflexes in Cats. *Neuroscience*, **113**, 435-447. https://doi.org/10.1016/S0306-4522(02)00173-2

[14] Craig, A.D. (1993) Propriospinal Input to Thoracolumbar Sympathetic Nuclei from Cervical and Lumbar Lamina I Neurons in the Cat and the Monkey. *Journal of Comparative Neurology*, **331**, 517-530. https://doi.org/10.1002/cne.903310407

[15] Cabot, J.B., Alessi, V., Carroll, J. and Ligorio, M. (1994) Spinal Cord Lamina V and Lamina VII Interneuronal Projections to Sympathetic Preganglionic Neurons. *Journal of Comparative Neurology*, **347**, 515-530. https://doi.org/10.1002/cne.903470404

[16] Dembowsky, K., Czachurski, J. and Seller, H. (1985) An Intracellular Study of the Synaptic Input to Sympathetic Preganglionic Neurones of the Third Thoracic Segment of the Cat. *Journal of the Autonomic Nervous System*, **13**, 201-244. https://doi.org/10.1016/0165-1838(85)90012-8

[17] Spanswick, D., Renaud, L.P. and Logan, S.D. (1998) Bilaterally Evoked Monosynaptic EPSPs, NMDA Receptors and Potentiation in Rat Sympathetic Preganglionic Neurones *in Vitro*. *The Journal of Physiology*, **509**, 195-209. https://doi.org/10.1111/j.1469-7793.1998.195bo.x

[18] Jiang, M., Alheid, G.F., Calandriello, T. and McCrimmon, D.R. (2004) Parabrachial-Lateral Pontine Neurons Link Nociception and Breathing. *Respiratory Physiology & Neurobiology*, **143**, 215-233. https://doi.org/10.1016/j.resp.2004.07.019

[19] Sneddon, L.U. (2015) Pain in Aquatic Animals. *Journal of Experimental Biology*, **218**, 967-976. https://doi.org/10.1242/jeb.088823

[20] Sneddon, L.U. (2004) Evolution of Nociception in Vertebrates: Comparative Analysis of Lower Vertebrates. *Brain Research Reviews*, **46**, 123-130. https://doi.org/10.1016/j.brainresrev.2004.07.007

[21] Dunlop, R. and Laming, P. (2005) Mechanoreceptive and Nociceptive Responses in the Central Nervous System of Goldfish (*Carassius auratus*) and Trout (*Oncorhynchus mykiss*). *The Journal of Pain*, **6**, 561-568. https://doi.org/10.1016/j.jpain.2005.02.010

[22] Smith, E.S. and Lewin, G.R. (2009) Nociceptors: A Phylogenetic View. *Journal of Comparative Physiology A. Neuroethology, Sensory, Neural, and Behavioral Physiology*, **195**, 1089-1106. https://doi.org/10.1007/s00359-009-0482-z

[23] Sneddon, L.U. (2018) Comparative Physiology of Nociception and Pain. *Physiology* (*Bethesda*), **33**, 63-73. https://doi.org/10.1152/physiol.00022.2017

[24] Guo, M., Wu, T.-H., Song, Y.-X., Ge, M.-H., Su, C.-M., Niu, W.-P., Li, L.-L., Xu, Z.-J., Ge, C.-L., Al-Mhanawi, M.T.H., Wu, S.-P. and Wu, Z.-X. (2015) Reciprocal Inhibition between Sensory ASH and ASI Neurons Modulates Nociception and Avoidance in *Caenorhabditis elegans*. *Nature Communications*, **6**, Article No. 5655. https://doi.org/10.1038/ncomms6655

[25] Osugi, T., Okamura, T., Son, Y.L., Ohkubo, M., Ubuka, T., Henmi, Y. and Tsutsui, K. (2014) Evolutionary Origin of GnIH and NPFF in Chordates: Insights from Novel Amphioxus RFamide Peptides. *PLoS ONE*, **9**, e100962. https://doi.org/10.1371/journal.pone.0100962

[26] Martin, A.R. and Wickelgren, W.O. (1971) Sensory Cells in the Spinal Cord of the Sea Lamprey. *The Journal of Physiology*, **212**, 65-83. https://doi.org/10.1113/jphysiol.1971.sp009310

[27] Yoshino, J., Morikawa, R.K., Hasegawa, E. and Emoto, K. (2017) Neural Circuitry That Evokes Escape Behavior upon Activation of Nociceptive Sensory Neurons in Drosophila Larvae. *Current Biology*, **27**, 2499-2504.e3. https://doi.org/10.1016/j.cub.2017.06.068

[28] Burgos, A., Honjo K., Ohyama, T., Qian C.S., Shin, G.J.-E., Gohl, D.M., Silies, M., Tracey, W.D., Zlatic, M., Cardona, A. and Grueber, W.B. (2018) Nociceptive Interneurons Control Modular Motor Pathways to Promote Escape Behavior in Drosophila. *Elife*, **7**, e26016. https://doi.org/10.7554/eLife.26016

[29] Hu, Y., Wang, C., Yang, L., Pan G., Liu, H., Yu, G. and Ye, B. (2020) A Neural Basis for Categorizing Sensory Stimuli to Enhance Decision Accuracy. *Current Biology*, **30**, 4896-4909.e6. https://doi.org/10.1016/j.cub.2020.09.045

[30] Sanders, J., Nagy, S., Fetterman, G., Wright, C., Treinin, M. and Biron, D. (2013) The *Caenorhabditis elegans* Interneuron ALA Is (Also) a High-Threshold Mechanosensor. *BMC Neuroscience*, **14**, Article No. 156. https://doi.org/10.1186/1471-2202-14-156